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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/682,303	10/09/2003	Raul Trillo	ANA 5955 (61834)	7332

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EXAMINER	
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ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
08/25/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/682,303	TRILLO ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5 and 7-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5 and 7-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/11/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continuation Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/11/10 has been entered.

Response to Arguments

This Office Action is in response to the amendment submitted on 08/11/10. Claims 1-2, 4-5, and 7-15 are currently pending in the application, with claims 3 and 6 having being cancelled. Accordingly, claims 78-136 are being examined on the merits herein.

Receipt of the aforementioned amended claims and Information Disclosure Statement (IDS) is acknowledged and has been entered.

Applicant's argument with respect to the 103 (a) rejection over Saito in view of Gray and Gelb has been fully considered. Applicant argues that the cited references whether taken alone or in any proper combination do not render obvious the claimed invention. Moreover, applicant argues that one of ordinary skill would not have a reasonable expectation of success. Such arguments are not persuasive as the Examiner maintains

that Saito in view of Gray and in further view of Gelb does indeed render obvious applicant's invention. Specifically, Saito et al. teach that when halothane was given to cats with induced permanent focal ischemia via left middle cerebral artery occlusion (MCAO), it prevented transient depolarizations from progressing to terminal depolarizations and reduced infarct volumes (see abstract). Saito et al. further teach that one explanation of the ameliorative effects of halothane may be due to reduction of ischemia-induced glutamate accumulation and that such decreased ischemic glutamate elevation by halothane (or isoflurane) could be responsible for the reduction of SD-like depolarizations and for infarct volume reduction. Saito does not teach parenteral administration of a halogenated volatile anesthetic, with an emulsification adjuvant and an emulsifier in a sub-anesthetic amount in the form of a bolus or an injection. Saito does however disclose that anesthetic agents can be formulated as a bolus or in injection form and can be administered continuously. Gray, on the other hand, was provided to demonstrate why one skilled in the art would formulate injection forms of anesthetic agents since Gray suggests the use of intravenous injections for rapid anesthetic induction effect. Moreover, Gray demonstrated that it is well known in the art to add emulsifying agents and emulsification adjuvants to injection formulations of halogenated volatile anesthetics. Consequently, one of ordinary skill in the art would have found it obvious to add the emulsification adjuvants and agents to the composition of Saito since Gray teaches that such ingredients is commonly added to intravenous injections of halogenated volatile anesthetics.

While applicant argues that Saito does not conclusively demonstrate a protective effect, the Examiner maintains that Saito explicitly stated that his halothane administration resulted in protection and that such protection was confirmed as a result of administration of α-choralose as a second treatment. Since the instant claims are not directed to a particular threshold for protective effects, the Examiner maintains that Saito does indeed render obvious applicant's invention. As for applicant's arguments that one skilled in the art would not have a reasonable expectation of success that the same drug administered via inhalation will be effective when administered as an injectable formulation, such arguments are not found persuasive since injectable forms of such formulations are well within the purview of the skilled artisan. Moreover, given that Gray provides the motivation for formulating such compositions as injections and in light of Saito who demonstrated effectiveness of the inhalable form of the formulation, the Examiner contends that formulating injections of the composition of Saito is within the skilled of the artisan and would have had a reasonable expectation of success since such formulations are known in the art and has been made effectively as taught by Saito. If however applicant disagrees with the fact that such formulation would result in an effective composition, it is incumbent upon applicant to demonstrate through side by side comparison that such compositions do not result in an effective formulation.

As for applicant's reference to Luchinetti, such reference is not found persuasive as Lucchinetti also teaches the advantageous reasons for formulating compositions for intravenous use (see pg. 1345, paragraph 2). Specifically, Lucchinetti teaches that

parenteral administration can 1) eliminate the need for specific ventilatory circuit; 2) can lead to rapid anesthetic induction and recovery; 3) can lead to hemodynamic stability; 4) can lead to administration of lower dosages; and 5) can reduced tissue toxicity (see Luchinetti, pg. 1345, paragraph 2). Consequently, the Examiner maintains in light of the teachings of Lucchinetti, one skilled in the art would have found it obvious to administer such formulation intravenously in light of the advantages associated with intravenous administration. Thus, regardless of the differences in pharmacokinetic properties, one skilled in the art would have found it obvious to try and administer such formulations intravenously if the desire is to lower the dosage given to patients and lower tissue toxicity.

As for applicant's arguments that Saito fails to teach administration of sub-anesthetic doses, such arguments are not found persuasive as the Examiner contends that the rejection was made over Saito in view of Gray and Gelb. Specifically, Gelb teaches that sub-anesthetic amounts result in patients being easily rousable and coherent while symptoms of hypoxaemia are markedly reduced or absent. Thus, one of ordinary skill in the art would have found it obvious to try the sub-anesthetic amount of halothane as taught by Gelb and one of ordinary skill in the art would have had a reasonable expectation of success since Gelb teaches that sub-anesthetic amounts simply reduce ventilatory responses thereby suggesting protective effects should necessarily be noticed at the lower amount. Determining the appropriate sub-anesthetic amount is well within the purview of the skilled artisan and can be determined during

routine experimentation. Moreover, the Examiner reminds applicant that nowhere in the disclosure of Gelb is it taught that sub-anesthetic amount is equated to being awake. In fact, Gelb teaches the use of halothane in patients undergoing dental surgery thereby suggesting that such patients were not in an awakened state. Additionally, the Examiner maintains that even if arguendo Gelb teaches administration of halothane in awake state, the purpose of Gelb was to determine the effects of halothane at various concentrations so that anesthetists can be aware of dosages to be administered to patients undergoing surgery. Consequently, the Examiner contends that one of ordinary skill in the art would have indeed found it obvious to administer halothane at a sub-anesthetic amount as taught by Gelb if the desire is to prevent impairment of ventilatory responses. Again, the Examiner contends that if applicants disagree with the fact that such protective effects purported by Saito would not occur if administered at sub-anesthetic amount, it is incumbent upon them to demonstrate through comparative data that such effects do not actually occur. The Examiner therefore reiterates that the rejection was indeed proper and is therefore maintained.

As for applicant's arguments regarding claims 14 and 15, such arguments are not found persuasive as applicant is arguing features not previously presented. It is noted that the features upon which applicant relies (i.e., patients in need of cardioprotection or neuroprotection) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification

are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Consequently, such arguments are moot.

For the foregoing reasons, the rejection of record under 103 (a) remains proper and is maintained. However, in view of applicant's amendment, the following 112, second paragraph and modified 103 (a) Non-Final rejection is being made.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **(see M.P.E.P 608.01 (k))**.

Claim 14 is particularly vague and indefinite given that applicant is claiming "cardiprotection" (**in sentence 2 of claim 14**). Given that applicant did not particularly point out what the particular term "cardiprotection" is referring to, one of ordinary skill in the art would not be able to fully ascertain the metes and bounds of the aforementioned claims.

As a result of the above inconsistencies, the aforementioned claim is unable to be examined as disclosed given that the scope of the claimed subject matter would not be able to be determined by one of ordinary skill in the art. However, for the sake of

compact prosecution, the Examiner will construe that applicant is referring to "cardioprotection".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
1. Determining the scope and contents of the prior art. 2. Ascertaining the differences between the prior art and the claims at issue. 3. Resolving the level of ordinary skill in the pertinent art. 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under

37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-5, 7-13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saito et al. (Reduction of Infarct Volume by Halothane: Effect on Cerebral Blood Flow or Perifocal Spreading Depression-Like Depolarizations, Journal of Cerebral Blood Flow and Metabolism, 1997, vol. 17, pp 857-864, previously submitted) in view of Gray et al. (GB2350297, previously submitted) in further view of Gelb et al. (Canad. Anaesth. Soc. J., November 1978, Vol. 25. No. 6, pgs. 488-494, previously submitted).

Saito et al. teach that when halothane was given to cats with induced permanent focal ischemia via left middle cerebral artery occlusion (MCAO), it prevented transient depolarizations from progressing to terminal depolarizations and reduced infarct volumes (see abstract). Thus halothane showed protective properties in studies of experimental brain ischemia (i.e. stroke; instant claims 1, 4-5, and 12). Saito et al. teach on page 2 of 12, that the cats treated with halothane were given halothane before, during and after the MCAO (up to 16 hours; instant claims 7-9; see pg. 2, last paragraph, and pg. 3, first paragraph). Particularly, Saito et al. teach that halothane anesthesia was kept as described throughout the entire experimental protocol

suggesting that halothane was administered continuously during the experimental procedure (see pg. 3, first paragraph). Saito et al. also teach that in the α-chloralose group, a bolus was administered intravenously after preparation of the animals and to keep continuous α-chloralose anesthesia, a continuous infusion was started after the initial bolus was injected (see pg. 3, paragraph 1). Saito et al. further teach, on page 9 of 12, that one explanation of the ameliorative effects of halothane may be due to reduction of ischemia-induced glutamate accumulation similar to that seen with isoflurane. The decreased ischemic glutamate elevation by halothane (or isoflurane) could be responsible for the reduction of SD-like depolarizations and for infarct volume reduction. Importantly, Saito teaches that volatile anesthetics including halothane and sevoflurane, reduce brain damage in animals subjected to focal cerebral ischemia (see pg. 7, paragraph 3 and pg. 9, paragraph 3). This suggests that halothane would also confer protection to neurons (i.e. neuroprotection; instant claim 15) since the brain houses many neurons and given that Saito discloses that halothane reduce damage in the brain.

Saito et al. do not teach parenteral administration of a halogenated volatile anesthetic, with an emulsification adjuvant and an emulsifier in a sub-anesthetic amount. Similarly, Saito et al. do not teach a bolus or infusion administration of the halogenated volatile.

Saito et al., however, do teach that anesthetic can be administered as an injectable bolus or as an infusion for continuous anesthetic administration.

Gray et al. teach, in the abstract, an injectable anesthetic formulation comprising a halogenated anesthetic compound (such as halothane or isoflurane) and at least one emulsifier (see abstract and pg. 2, lines 22-30). Gray et al. also teach that while most halogenated anesthetics are administered by inhalation, such mode of administration can be relatively slow in some patients and the wearing of a mask for such anesthetics can be upsetting for some patients and therefore suggest intravenous injections for rapid anesthetic induction effect (see pg.1, lines 8-16). On page 3 of the publication, Gray et al. further teach that the formulations can include an emulsification adjuvant such as soybean oil and an emulsifier such as lecithin. Moreover, additional emulsifiers include polyoxypropylene/polyoxyethylene block co-polymers (see pg. 3, lines 25-30, and pg. 4, lines 1-10). Glycerol may be added as a tonicifier for adjusting the tonicity of the anesthetic formulation to the tonicity of the patient's blood plasma along with pH adjustors and water (see pg. 4, lines 23-30 and pg. 5, lines 1-7).

Gelb et al. teach that it is important for clinical anesthetists to know both the duration of action of drugs and their effects in all concentrations (see pg. 488, left col., paragraph 1). Gelb et al. further teach that general halothane administration can depress the ventilatory response and affect heart rate but sub-anesthetic amounts (i.e. 0.1 MAC or 0.05 MAC; which necessarily reads on applicant's definition of sub-

anesthetic amount of halothane as delineated on pg. 4, lines 19-26) result in patients being easily rousable and coherent while symptoms of hypoxaemia are markedly reduced or absent (see pg. 489, left col., paragraph 2, right col., last paragraph and table 1). Importantly, Gelb et al. teach that general anesthetic effect may impair the ventilatory responses but low doses (i.e. sub-anesthetic amount; instant claim 1) markedly reduce such responses (see pg. 493, Summary Section).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the halogenated volatile anesthetic (HVA), halothane, in the method of treating ischemia since Saito et al. teach that halothane and isoflurane (two volatile halogenated anesthetics) have shown protective effects in experimental ischemia. Further it would have been obvious to administer the volatile halogenated anesthetics parenterally as Gray et al. teach that volatile halogenated anesthetics including halothane and isoflurane can be administered in such a manner when using an emulsifier and an emulsifier adjuvant. Likewise, one of ordinary skill in the art would have found it obvious to administer the HVA as a bolus or as an infusion as Saito et al. demonstrated that other anesthetics (i.e. α-chloralose) can be administered in such a way and Gray et al. teach parenteral formulations of halothane or administer the HVA in a sub-anesthetic amount since Gelb et al. teach that low dose halothane administration avoids effects on ventilatory responses.

Regarding the method of treating a heart tissue delineated in claim 13, it is considered obvious for one of ordinary skill in the art to pursue known options within his or her technical grasp. Given that heart and brain tissues can both undergo similar ischemic insults, one of ordinary skill in the art would have been motivated to try halothane in both tissues with a reasonable expectation that halothane will produce similar results in the tissues of the heart.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saito et al. (Reduction of Infarct Volume by Halothane: Effect on Cerebral Blood Flow or Perifocal Spreading Depression-Like Depolarizations, Journal of Cerebral Blood Flow and Metabolism, 1997, vol. 17, pp 857-864, previously submitted) in view of Gray et al. (GB2350297, previously submitted) in further view of Gelb et al. (Canad. Anaesth. Soc. J., November 1978, Vol. 25. No. 6, pgs. 488-494, previously submitted) as applied to claims 1-2, 4-5, 7-13, and 15 and in further view of Gallagher et al. (Anesthesia & Analgesia, 1998, Vol. 86, pgs. 488-492).

The Saito, Gray, and Gelb references are as discussed above and incorporated by reference herein. Saito, Gray, and Gelb do not however teach that the method of treating with halothane results in cardioprotection.

Gallagher et al. teach that the goal of his studies was to clarify the effects of halothane on abnormal automaticity (i.e. spontaneous beating of cardiac cells with

abnormally depolarized resting membrane potentials; see abstract). Importantly, Gallagher et al. teach that halothane administration reduced the rate of firing by those cardiac cells (i.e. cardiac tissue) in a dose-dependent manner wherein abnormal automaticity was abolished and/or reduced (see abstract). This suggests that halothane provided cardioprotection when administered in a dose-dependent manner.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the halogenated volatile anesthetic (HVA), halothane, in the method of treating cardiac ischemia since Saito et al. teach that halothane and isoflurane (two volatile halogenated anesthetics) have shown protective effects in experimental ischemia and in view of Gallagher who teach that halothane provides cardioprotective effects against cardiac automaticity. Thus, give the teachings of Saito, Gray, Gelb, and Gallagher, one of ordinary skill in the art would have been motivated to utilize the halothane of Saito for cardioprotective effect with the reasonable expectation of success in providing a method that is effective in treating cardiac tissue.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1627

08/19/2010

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627